Practical Screening for Islet Autoantibodies: The Time Has Come

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KEY TAKEAWAYS

- The increasing prevalence of type 1 diabetes (T1D) suggests family physicians will regularly see first-degree relatives of patients with T1D with the genetic propensity for developing T1D.
- T1D autoantibody screening by family clinicians addresses an important need to identify at-risk individuals early and achieve short- and long-term health benefits.
- Multiple T1D screening options and programs are available to clinicians that provide patient education, testing, result analysis, follow-up, and opportunity for participation in T1D prevention trials.
- The provider-patient relationship in family medicine places clinicians in a unique position to provide monitoring and follow-up crucial to family members with positive autoantibody results.

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According to the Centers for Disease Control and Prevention's (CDC) National Diabetes Statistics Report (2020), 1.6 million adults and 244,000 youth under 20 years of age have type 1 diabetes (T1D).[1] Estimated prevalence per 1000 youth has increased from 1.48 in 2001 to 2.15 in 2017.[2] During the COVID-19 pandemic, the incidence increased significantly in individuals <18 years, suggesting an associated risk requiring ongoing evaluation.[3] Combined with the fact that T1D is a common chronic disease in children, it is highly probable that at-risk individuals, particularly relatives, are present in nearly every primary care practice. Autoantibody screening and monitoring in relatives has potential short- and long-term health benefits to these at-risk relatives.[4] Benefits include early diagnosis, reducing the risk of life-threatening diabetic ketoacidosis (DKA), and reducing short- and long-term complications of clinical diabetes.[4-6] In addition, the future holds promise of therapies that may delay or even prevent clinical T1D.

The progression of beta-cell destruction to the eventual development of clinical T1D is a continuum that progresses over months to years.[7-9] Long before the manifestation of symptoms, the disease is present in 3 well-defined stages corresponding to beta-cell loss.[10] In stage 1, ≥2 islet autoantibodies are present, indicating T1D, but normoglycemia is maintained. Stage 2 is characterized by ≥2 autoantibodies and progression to dysglycemia (impaired glucose tolerance). Stage 3 represents the onset of clinical T1D and overt hyperglycemia, requiring exogenous insulin.

The rate of progression varies between individuals and is influenced by variables including the age islet autoantibodies develop and number of autoantibodies.[11,12] Young children are more likely to experience rapid beta-cell destruction than adolescents or adults and are at the greatest risk of developing life-threatening DKA at diagnosis.[8,11,12] Destruction can be gradual, as adults may retain enough beta-cell function to slow progression to clinical T1D for years.[9]

BENEFITS OF SCREENING

Measuring autoantibodies in relatives represents targeted screening to identify who may eventually develop T1D.[9,10] The presence of ≥2 islet autoantibodies is a near certain predictor of clinical T1D; 69.7% of children develop T1D by 10

years and nearly all (84.2%) by 15 years of follow-up.[9,10] Progression is most rapid in children with multiple autoantibodies before age 3.[9]

Clinical T1D presents with life-threatening DKA 40% to 60% of the time at diagnosis and results in longer and more burdensome hospitalizations.[13,14] Since the mortality rate from DKA is 0.2% to 2.0%, preventing DKA is an important goal. During the COVID-19 pandemic, the increased incidence of T1D among US children was accompanied by an increase in DKA.[3,15] Two US medical claims databases reported a significant increase in new T1D diagnoses (166% and 31%) among patients with COVID-19, and nearly half had DKA at diagnosis.[3]

Early risk identification coupled with monitoring, counseling, and diabetes education enables earlier diagnosis and lowers the risk of DKA. In the Diabetes Prevention Trial (DPT-1), 63.3% of asymptomatic participants were diagnosed early based on laboratory parameters, including autoantibody testing, and only 3.67% developed DKA.[16] In the Diabetes Autoimmunity Study in the Young (DAISY), only 3% of children were hospitalized with DKA at diagnosis compared with 44% from the age- and-sex-matched community.[17] Children in The Environmental Determinants of Diabetes in the Young (TEDDY) study were also significantly less likely to experience DKA at diagnosis compared with a comparable population.[18]

Preventing DKA has more than short-term clinical benefits. Preventing DKA at diagnosis increases the likelihood of partial remission (the honeymoon phase) of T1D, characterized by dramatically reduced insulin requirements, and is associated with better long-term metabolic control and lower insulin requirements.[4,5,19] Thus, preventing or delaying individuals moving from stage 1 to stage 3 T1D would have enormous health benefits. Furthermore, ongoing clinical trials examining disease-modifying methods of treating autoantibody-positive individuals in stage 2 have the potential to prevent or delay the diagnosis of stage 3 clinical T1D.[20-22] For these reasons, the American Diabetes Association (ADA) offers this recommendation:

> *Screening for presymptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2A), and zinc transporter 8 (Znt8A) is currently recommended in the setting of a research study or can be considered an option for first-degree family members of a proband with type 1 diabetes.*[21]

SCREENING CONVERSATIONS

While genetics play a key role in the pathogenesis of T1D, only 10% to 20% of cases occur in individuals with a family history.[23,24] Nevertheless, targeted screening of at-risk family members is practical and beneficial. Family members of patients with T1D have approximately a 15-fold increased risk (1:20), compared with the general population risk of 1:300.[9,21]

The CDC advocates for increased surveillance for T1D in US youth, particularly minority populations, as steeper increases were observed from 2002 to 2015 among blacks (2.7%/year), Hispanics (4%/year), and Pacific Islanders (4.4%/year) than among whites (0.7%/year).[2] The peak incidence for development of islet autoantibodies occurs in the first few years of life, generally between 3 and 5 years of age, with sensitivity peaking at 4 years.[23-25] Age 3 to 4 years has been suggested as the best time to screen children using islet autoantibody testing.[24,25] Yet concern exists that this would miss the youngest children. Vigilance in monitoring youth in at-risk families is important as diagnosis can occur at any age but is most often in youth 10 to 14 years of age.[26,27]

Family physicians are trusted sources of information for their patients and families. Shared decision-making occurs at every step of the T1D screening journey, beginning with the discussion of whether an individual wants to know their own or a loved one's risk of developing T1D. The psychological impact of a positive result can be a source of stress and anxiety that may offset the benefit of an early diagnosis.[28-30] Parents could impair family well-being by treating a child differently in an attempt to control environmental risk factors.

Parents of children receiving positive autoantibody test results exhibit high anxiety scores.[28-30] Mothers have higher anxiety than fathers, and mothers from families with T1D exhibit significantly greater anxiety (P = .002) than mothers from the screened general population. This implies that knowing the burden of T1D may increase anxiety. Uncertainty about when stage 3 T1D will develop in children with multiple autoantibodies, along with the feeling that parents cannot do anything to prevent it, can lead to high anxiety. While anxiety declines over the years, parents of children with multiple autoantibodies continue to experience long-term high anxiety.[29]

Fortunately, integrating basic diabetes education, counseling, and access to mental health professionals in families with multiple positive islet autoantibody results yields long-term positive effects on anxiety.[28-30] This is encouraging as it reinforces that clinicians who adequately prepare individuals, as suggested in **TABLE 1,** can lower anxiety risk in families.[31]

AUTOANTIBODY SCREENING OPTIONS

A panel of islet autoantibodies is recommended over individual tests to ensure that an autoantibody that may be predic-

TABLE 1. **Autoantibody screening process**

Initial discussion
Risk of developing T1D
Benefits and risks of testing: early diagnosis, prevent DKA, reduce risk for clinical disease, potential to participate in prevention trials or therapeutic options
Psychological impact of screening results
Refer to JDRF T1Detect, TrialNet, or askhealth.org for resources
Screening
Commercial laboratory (physician order required)
TrialNet (no prescription, screen families of T1D patients)
JDRF, T1Detect (no prescription, screens regardless of family history)
Regional programs (ASK, PLEDGE, CASCADE)
Follow-up/monitoring
Results and risk implications
Confirming autoantibody tests
Metabolic testing
Diabetes education
Evaluation and follow-up
Emotional support/resources
Clinical trials and therapy options
Endocrinologist consult

Source: Adapted from Type 1 Diabetes TrialNet. TrialNet Recommendations for clinicians. Accessed Arpil 15, 2022. https://www.trialnet.org/healthcare-providers

tive is not missed: autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), islet antigen 2 (IA-2A), and zinc transporter 8 (Znt8A).[22] Average clinical sensitivity and specificity of assays are 96% and 97%, respectively, and have been reported to correctly identify 95% of high-risk individuals with ≥2 autoantibodies.[32]

Clinicians can screen at-risk relatives in their clinical practice by ordering screening panels from commercial laboratories (the cost of which is dependent on insurance availability and coverage). Laboratories offering autoantibody screening panels include Mayo Laboratories, LabCorp, and Quest Diagnostics.[33] Interpretation and next steps are determined by the prescribing practitioner. A useful guideline is suggested by the JDRF (formerly Juvenile Diabetes Research Foundation) in **TABLE 2.**[33]

T1Detect (JDRF.org) offers patients autoantibody screening, education before and after testing, and guidelines for follow-up. Access is available to anyone, regardless of family history. A physician order is not required to obtain a test kit. The test uses a finger-prick blood sample. Three markers are measured: IAA, GADA, and IA-2A. Results and interpretation are returned to the patient with suggestions for discussing results with their clinician.[33]

TrialNet (https://trialnet.org/), a National Institutes of Health–funded network of researchers, clinicians, and academic institutions, is dedicated to understanding the natural history of T1D and preventing or delaying the disease.[21,34] TrialNet provides free autoantibody screening kits to relatives for in-home testing or taking to their local laboratory. TrialNet testing sites are also available. Results and interpretation are returned in 4 to 6 weeks. Autoantibody-positive individuals can participate in follow-up and clinical trials, including prevention trials. TrialNet and T1Detect offer resources for both healthcare professionals and participants.

Free regional screening programs that do not require a physician order are presented here:

- **ASK,** Autoimmunity Screening for Kids, open to Colorado children ages 1 to 17 years, with or without a family history: https://www.askhealth.org/childhood-diabetes
- **PLEDGE,** a screening program available to children under 6 years of age at Sanford Health System, South Dakota: https://www.sanfordhealth.org/medical-services/pediatrics/pediatrics-specialized-care/pledge
- **CASCADE,** screening for T1D in children from birth to 8 months and 4 to 8 years in Washington state: https://cascadekids.org/

FOLLOW-UP

Explaining results to patients and families involves correlating the number of autoantibodies with approximate risk for developing T1D. Participants will present with either no autoantibodies, 1 detected autoantibody, or ≥2 autoantibodies.

Individuals with no antibodies are at low risk for developing T1D. While this does not mean they will not develop T1D, data from TrialNet suggest it is uncommon. Testing positive for a single autoantibody is associated with a 14.5% risk of progressing to T1D in 10 years.[8-11] However, some children <5 years of age may progress faster if the single autoantibody is IA-2A.[10]

Individuals in stage 1 T1D have a 44% risk of progressing to clinical T1D within 5 years and 70% within 10 years.[9] If the disease has progressed to include dysglycemia (stage 2), individuals have a 60% risk in 2 years and a 75% risk in 4 to 5 years.

MONITORING

Currently, there are no evidence-based guidelines for

TABLE 2. **Monitoring after T1D autoantibody screening**

Results	Monitoring
Autoantibody negative	Rescreen • If symptomatic • At age 5 years, if previously screened • 11 years if screened between 5 and 10 years of age
1 autoantibody positive	• Rescreen • HbA1C for normality (<5.7%) • Metabolic testing in 6 months to exclude clinical T1D (OGTT, FPG, random BG) • If single autoantibody-positive for 2 years, rescreen annually
≥2 autoantibodies positive	Stage 1: Normoglycemia (HbA1C <5.7%) • Rescreen • Exclude clinical (stage 3) T1D diagnosis • Follow up in 6 months to exclude clinical T1D diagnosis (OGTT, FBG, random BG) • Educate regarding signs and symptoms Stage 2: Dysglycemia confirmed – Fasting plasma glucose 100-125 mg/dL – 2-hour plasma glucose 140-199 mg/dL – HbA1C 5.7%-6.4% • Rescreen • Fasting blood glucose and 2-hour post largest meal BG once weekly (CGM or test strips) • BG >200 mg/dL consult endocrinologist • At 3 months, repeat autoantibodies, exclude T1D diagnosis with metabolic testing • T1D education Stage 3: Symptomatic diabetes • Assess: polyuria, polydipsia, weight loss, DKA • Exogenous insulin treatment • Consult endocrinologist

Abbreviations: BG, blood glucose; CGM, continuous glucose monitoring; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.
Source: Adapted from JDRF.org. T1Detect: learn why you should be screened. Accessed April 24, 2022. https://www.jdrf.org/t1d-resources/t1detect/

monitoring individuals with islet autoantibodies. However, based on published T1D screening studies, practical stage-specific recommendations are available at https://www.askhealth.org/experts. Next steps for patients and families after screening for T1D autoantibodies can be found here: https://1x5o5mujiug388ttap1p8s17-wpengine.netdna-ssl.com/wp-content/uploads/2021/07/TalkingtoPatientsandFamiliesAboutT1DRiskandScreeningTests-.pdf?_ga=2.256589835.1689151409.1647704787-2006460947.1628718247.[33]

Any positive autoantibody screening test result should be confirmed within 2 to 6 weeks.[8,27] Monitoring for symptoms of T1D is recommended in all at-risk individuals. In addition to stage-specific recommendations, a diagnosis of T1D is excluded with metabolic testing (**TABLE 2**).[35]

Metabolic testing criteria are used to identify the gradual metabolic deterioration in beta-cell function.[34,35] Tests include:

- **Glycated hemoglobin (HbA1C):** Recommended for all at-risk patients. Increasing levels of HbA1C above baseline (≥10%) or A1C of 5.7% to 6.4% serve as a biomarker of progression to T1D.
- **Oral glucose tolerance test (OGTT):** The 2-hour

glucose value in an OGTT predicts progression as early as 1.45 years prior to T1D.[36] However, in the TEDDY study, only 6% of children under 3 years were diagnosed by an OGTT.[23]

- **Fasting plasma glucose (FPG):** FPG and a 2-hour plasma glucose identify impaired glucose tolerance and diagnose diabetes. The 2-hour plasma glucose is optimal.[36]
- **Random plasma glucose:** A random plasma glucose >200 mg/dL is diagnostic of diabetes in symptomatic individuals and used in stage 2 as a call to action if asymptomatic.
- **C-peptide levels:** Fasting C-peptide and stimulated levels are not recommended in screening as they lag behind changes in the OGTT.

Recently, a composite screening measure known as Index60 using fasting C-peptide, 60-minute C-peptide, and a 60-minute serum glucose has been proposed as an option in stage 2 to identify individuals with declining beta-cell function who would otherwise be missed on an OGTT.[37] The premise is that if dysglycemia is the only criterion for stage 2, a substantial group with normoglycemia would lose the opportunity for intervention.

In the DAISY study, time spent with glucose values >140 mg/dL (time above 140 [TA140]; 7.8 mmol/L) predicted progression to diabetes in autoantibody-positive children.[38,39] Continuous glucose monitoring reports time above target blood glucose levels. The ASK study found TA140 >10% was associated with a high risk of progression to clinical diabetes within 1 year in autoantibody-positive children.[38] Continuous glucose monitoring has the potential to provide easier monitoring of at-risk individuals if more studies confirm these data.

While monitoring (particularly OGTT) can be burdensome, the patient-primary care clinician relationship can enhance follow-up. Children are more likely to maintain monitoring than adults (70.4% vs 58.2%) as are individuals with a proband with T1D.[34] Enrollment in a clinical trial with the possibility of therapeutic benefit is also considered motivating.[34]

CONCLUSION

The prevalence of T1D is increasing in the United States, with cases in youth of diverse populations growing at the fastest rate. Identifying the progression of T1D early is an important part of primary prevention strategies. Given that the disease process can be detected through autoantibody testing, family physicians have an opportunity to initiate screening of relatives, particularly children, of individuals with T1D and potentially impact the course of the disease. Once staged, monitoring and follow-up can lead to early detection, reduce likelihood of DKA, and reduce long-term metabolic complications of the disease. If preventative therapies are approved in the future, primary care clinicians will be able to guide treatment of autoantibody-positive relatives as well. ●

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